HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

CABLIVI (caplacizumab), antithrombotic

High clinical benefit in the treatment of acquired thrombotic thrombocytopenic purpura and minor clinical added value over standard treatment of the episode involving plasma exchanges combined with immunosuppressors.

Main points

- CABLIVI has been granted a marketing authorisation for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP) in conjunction with plasma exchange and immunosuppression.
- In a randomised double-blind study, CABLIVI was superior to the placebo, in addition to plasma exchanges (PE) and immunosuppression, in time to platelet count normalisation (primary biological endpoint), with an additional effect size considered modest.
- CABLIVI was statistically superior to the placebo for one of the ranked secondary endpoints, i.e. the percentage of patients with a recurrence of aTTP episode (including exacerbation or relapse), with 12.7% versus 38.4% (p<0.001), which was clinically relevant. Nevertheless no effect of CABLIVI over the placebo was demonstrated on other clinically relevant endpoint such as visceral pain or lethality.
- The safety profile is characterised by epistaxis, gingival bleeding, contusion and haematuria, with follow-up limited to the duration of the phase III study, i.e. 65 days.

Therapeutic strategy

- An aTTP episode is particularly serious, potentially leading to ischaemic events with significant clinical outcome, including stroke, myocardial infarction, kidney failure and short-term life threatening if no specific plasma therapy treatment is implemented (in more than 80% of cases). In longer term, these ischaemic events may also cause cardiovascular, renal and above all neurological sequelae, leading to a degradation of quality of life. aTTP requires rapid diagnosis, its management constituting a therapeutic emergency for which daily PEs should be rapidly initiated in combination with immunosuppression (usually corticosteroids ± rituximab [off-label used]). The confirmation of the disease diagnosis, provided by the ADAMTS13 activity dosage, is posterior to emergency treatment implementation.
- **Role of the medicinal product in the therapeutic strategy**
  CABLIVI is active against the initial phase of microthrombi formation, although it has no effect on the ADAMTS13 deficiency characteristic of this disease. CABLIVI must therefore be initiated early during standard therapy including plasma exchanges and immunosuppression, upon clinical presumption of an aTTP episode, without waiting for confirmation.
  CABLIVI is initiated by intravenous injection prior to plasma exchange, then continued by daily subcutaneous administration after completion of each plasma exchange, for the duration of daily plasma exchange treatment, followed by daily subcutaneous injections for 30 days after stopping daily plasma exchange treatment. For patients in clinical remission and whose ADAMTS13 activity has normalised before the end of the 30-day post-PE period, no data on the consequences on an early discontinuation treatment are available.
  If, at the end of this 30-day period, there is evidence of unresolved immunological disease, it is recommended to optimise the immunosupression regimen and continue daily subcutaneous administration of 10 mg of caplacizumab until the signs of underlying immunological disease are resolved (e.g. sustained normalisation of ADAMTS13 activity level).

Clinical data

- In one phase III, randomised, double-blind study versus placebo 145 patients were randomised (n=72 in the caplacizumab group and n = 73 in the placebo group) (ITT population), most of whom were female (69.0%), and of a mean age of 46 years. Almost of all patients (97.2% in the caplacizumab group and 97.3% in the placebo group) received immunosuppressive treatment. The primary endpoint result showed a statistically significant reduction in time to platelet count response in favour of the caplacizumab group compared to the placebo group (HR=1.55 [1.095; 2.195]; p=0.0099). The median was of 2.69 days, CI95% [1.89; 2.83] versus 2.88 days, CI95% [2.68; 3.56] in the placebo group, i.e. a difference of only 4 hours and 30 minutes. The ranked secondary endpoint results showed a significant reduction in the composite endpoint (aTTP-related death, aTTP exacerbation, or major thromboembolic event during the treatment period) in favour of caplacizumab: 12.7% versus 49.3%, p<0.0001. This reduction was mainly driven by less frequent aTTP exacerbations in the caplacizumab group compared to the placebo group (4.2% versus 38.4%) and no death under caplacizumab (0% versus 4.1%). The proportion of patients with a recurrence of aTTP (exacerbation or relapse) was significantly lower in the caplacizumab group than in the placebo group (12.7% versus 38.4%; p<0.001). No statistically significant differences were found on proportions of refractory patients during the double-blind treatment period.
- For patients treated with caplacizumab, the adverse effects reported in more than 5% of patients were as follows: epistaxis (28.9%), gingival bleeding (17.5%), catheter site haemorrhage (13.4%), TTP (12.4%), petechiae (7.2%), contusion (7.2%), ecchymosis (5.2%), haematoma (5.2%) and vaginal haemorrhage (5.2%). A smaller proportion of patients reported a thromboembolic event in the caplacizumab group (19.7%) than in the placebo group (50.7%).

Special prescription requirements

- Medicinal product subject to hospital prescription.

Benefit of the medicinal product

- The actual clinical benefit* of CABLIVI is high.
- CABLIVI provides a minor clinical added value** (CAV IV) over the standard treatment of aTTP episodes, including plasma exchanges combined with immunosuppression.
- Approval for hospital treatment.

HAS
HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 20 February 2019 (CT-17389) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".